Successful bone marrow transplantation in a patient with Schimke immuno-osseous dysplasia

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Early death in Schimke immuno-osseous dysplasia often results from renal failure and/or cell-mediated immunodeficiency. Kidney transplants have improved renal function, but effective therapy for the immunodeficiency has not yet been reported. We describe markedly improved marrow function 2 years after bone marrow transplantation in a boy with Schimke immuno-osseous dysplasia. (J Pediatr 2000;137:882-6)

Schimke immuno-osseous dysplasia is a rare autosomal recessive early childhood skeletal dysplasia first described in 1974.[1-5] Classically, it is characterized by variable multisystem medical problems including spondyloepiphyseal dysplasia; in utero and postnatal growth retardation; proteinuria progressing to nephrosis and renal failure; mild facial dysmorphisms; lymphopenia, pancytopenia, and defective cellular immunity with recurrent infections; and frequent autoimmune disease (Table). Neurocognitive function is usually normal, but cerebrovascular abnormalities (eg, cerebral ischemia and/or moyamoya disease) sometimes develop.[4,6,7] The molecular basis is unknown. Autosomal recessive inheritance is suggested by the observed equal sex distribution, affected siblings, and consanguinity.[3,4] No cytogenetic or biochemical abnormalities provide insight into its etiology.

Progressive multisystem problems result in significant morbidity and early death. Nearly half of all affected individuals die before 16 years of age, often because of renal failure, immunodeficiency, or cerebral vascular disease.[3,4] A milder juvenile form of SIOD is associated with survival into early adulthood.[3,4,8,9] No curative therapy for SIOD exists. Kidney transplantation has improved renal function in some cases, but not hematologic function or other systemic manifestations. Treatment for hematologic manifestations, including erythropoietin, transfusions, and granulocyte colony-stimulating factor, is of limited value.[3,4] In fact, in an extensive analysis of SIOD, Boerkoel et al[4] did not identify any effective therapies for the growth failure, lymphopenia, hematologic manifestations, and cerebral ischemia. They suggested that bone marrow transplantation in addition to kidney transplantation might be effective. Clearly, BMT has been successful in the management of several childhood immunodeficiency syndromes and hypoplastic marrow states.[10-16] In immunodeficiency disorders with multisystem features, such as cartilage hair hypoplasia syndrome, BMT has improved immune function but not skeletal manifestations.[13] To date, there are no reports of BMT therapy in individuals with SIOD.

We describe a boy in whom SIOD was diagnosed at 6.5 years of age. Because bone marrow hypoplasia with severe progressive neutropenia, lymphopenia, and immune deficiency significantly contributed to his morbidity, he received an allogenic BMT, which resulted in successful trilineage reconstitution of his marrow, followed by kidney transplantation.

BMT	Bone marrow transplant
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GVHD	Graft-versus-host disease
SIOD	Schimke immuno-osseous dysplasia

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CASE REPORT

The patient was the 3 lb 7 oz, 14-inch product of a 34-week gestation, born to a 29-year-old healthy woman (gravida 2, para 1) without known teratogen exposures. He was delivered by cesarean section because of decreased movement and oligohydramnios. He had intrauterine growth retardation, bilateral cryptorchidism, and a crossed fused ectopic right-sided kidney (without renal impairment) but was otherwise healthy. Maternal relatives had short stature and cancer, but there was no significant family history of renal disease, immunodeficiency, hematologic problems, or skeletal dysplasias (Fig 1).

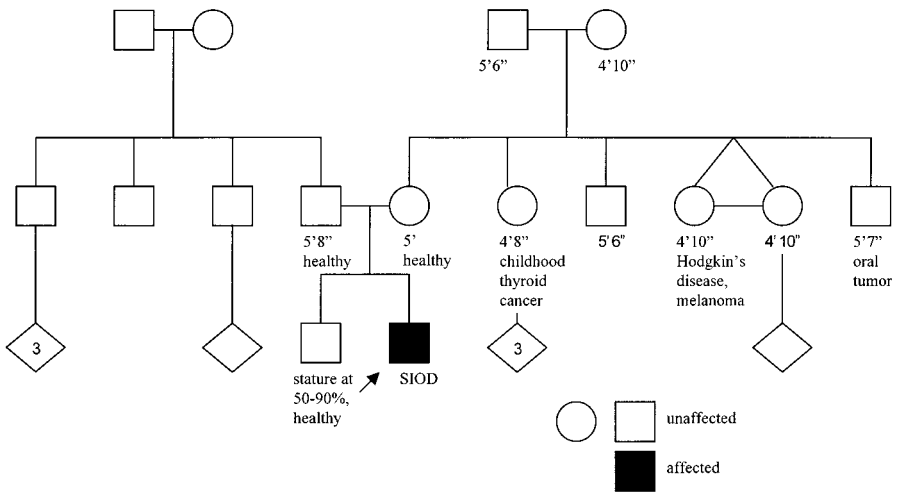

Fig 1. Pedigree of proband *(arrow)* with SIOD. His mother is of Irish ancestry and his father is of mixed European ancestry. There is no consanguinity. An older brother of normal stature is healthy. His father is average size and healthy. His mother has mild multiple sclerosis and stands just below the 3rd percentile for adult female height. Her family history is significant for mild non-syndromic proportionate short stature and cancer. There are no individuals with a constellation of findings consistent with SIOD.

Although his cognitive development was normal, he exhibited marked growth retardation with height and weight below the 3rd percentile since birth and head circumference between the 25th and 50th percentiles. He had failure to thrive with intermittent anorexia, nausea, and vomiting throughout childhood. Results of gastrointestinal, neurologic, and endocrine evaluations were normal. Bone ages at 3 and 6 years were chronologically appropriate.

At 4 years of age, he developed proteinuria that progressed to nephrotic syndrome. An open renal biopsy demonstrated minimal focal and segmental mesangial proliferation and IgG, IgA, IgM, C3, and C1Q deposition, consistent with immune complex nephritis. Antinuclear antibodies, C3 and C4 levels, and erythrocyte sedimentation rates were normal. Angiotensin-converting enzyme inhibitor therapy was begun to decrease proteinuria.

At 4.25 years of age, persistent neutropenia (absolute neutrophil count of 874/mm^3) was found. His bone marrow displayed 30% trilineage hypocellularity. Results of investigations for bone marrow failure syndromes were negative. A peripheral blood karyotype (46,XY) and results of metabolic assays and mitochondrial studies were normal. He developed multiple systemic infections, prompting a G-CSF trial, which normalized his absolute neutrophil count. Lymphopenia with T-cell depletion (CD3, CD4, and CD8 deficiencies) and spared B-cell function progressed. These findings along with mild dysmorphic features and radiographic evidence of spondyloepiphyseal dysplasia suggested the diagnosis of SIOD (Table, Fig 2).

At 6 years of age, he underwent an allogenic BMT. His conditioning therapy consisted of oral busulfan (4 mg/kg/d, day –9 to day –6) and intravenous cyclophosphamide (50 mg/kg/d, day –5 to –2). Graft-versus-host disease prophylaxis consisted of intravenous tacrolimus (0.03 mg/kg/d) and methotrexate (days 1, 3, 6, and 11). Engraftment occurred (absolute neutrophil count >500/mm^3) on day 12, but acute GVHD (grade III skin, grade IV GI) developed on day 26. His GI-GVHD failed to respond to methylprednisolone (2 mg/kg/d) and intravenous mycophenolate (1500 mg/m^2/d). He did not tolerate anti-thymocyte globulin. Intravenous administration of octreotide was begun but failed to decrease GI bleeding. Because of progressive GI-GVHD, anti-CD2 monoclonal antibody therapy, beginning on day 72 and ending on day 138, was given and led to resolution of GI-GVHD. Intermittent anorexia, nausea, and vomiting required transpyloric gastrojejunal tube feedings.

His post-transplantation course was further complicated by malignant hypertension with signs of hypertensive encephalopathy as determined by magnetic resonance imaging. Prolonged steroid therapy resulted in decreased bone maturation and growth (bone age 2 SD below the mean at 8 years) and diabetes. His course was significantly complicated by progressive nephrotic disease requiring albumin infusions and aggressive anti-hypertensive therapy. By 7 months after transplantation, he required hemodialysis. At 20 months after transplantation, he received a kidney from his father.

At 25 months after BMT (6 months after kidney transplantation), he was doing very well with full hematologic engraftment (25% trilineage cellularity with full maturation of 100% donor cells), normal renal function, normal neurocognitive function, no symptomatic immune problems, normal lymphocytes with subnormal quantitative CD3, CD4, and CD8 levels (CD3 390,

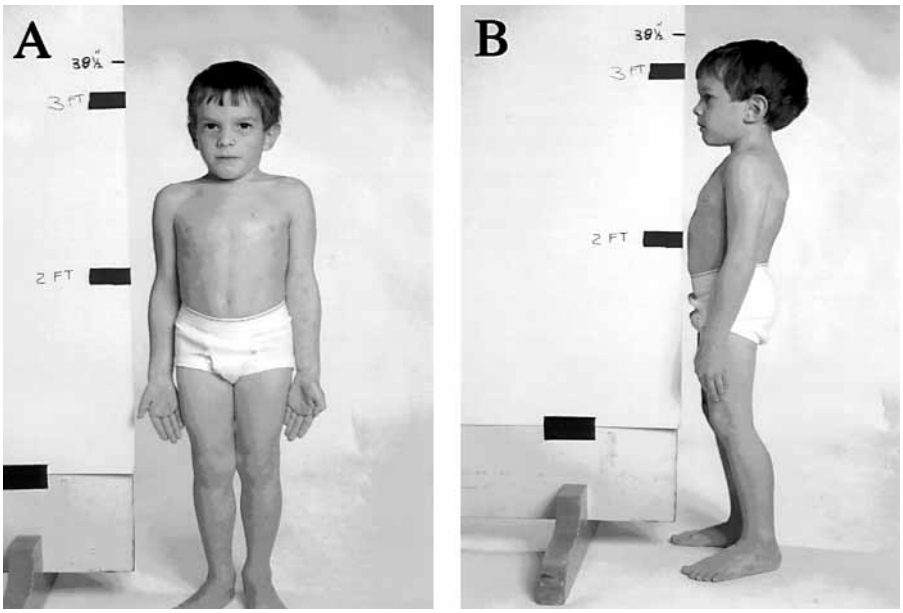

Fig 2. Frontal and side views of boy with SIOD at 6 years of age. Note his relative macrocephaly; mild facial dysmorphisms including a prominent brow with a broad forehead, well-defined facial features, a relatively small pointed chin, and triangular shape of the face; mild to moderate lumbar lordosis; mildly protuberant abdomen, and relatively short neck and trunk. He also had hypoplastic teeth, visible vascular markings on his abdomen, a normal penis with no palpable scrotal testicles, a slight decrease in full elbow extension bilaterally, mild fifth digit clinodactyly bilaterally, scattered freckles, a few nevi, and small brown macules consistent with small café au lait spots or larger freckles on his abdomen. Findings on neurologic examination were normal.

CD4 270, CD8 76), and marked subjective improvement over pre-BMT baseline.

DISCUSSION

This boy presented with prenatal and postnatal growth failure, a congenital structural renal anomaly, cryptorchidism, and various GI problems. Subsequent findings of nephrotic syndrome, neutropenia, T-cell lymphopenia, spondyloepiphyseal dysplasia, and mild dysmorphic features led to consideration of several bone marrow failure and genetic syndromes. The diagnosis of SIOD fit best because he had characteristic manifestations (Table). Of 39 individuals with SIOD, only one had a congenital renal anomaly[17] and one had GI symptoms similar to those of our patient.[18] Neutropenia was an early major finding in our patient. It is seen in 40% of individuals with SIOD.[3,4] Like others, our patient lacked immunoglobulin abnormalities, and recurrent infections were consistent with cell-mediated immune dysfunction with T-cell lymphopenia. This was predicted to worsen, given the progressive marrow failure observed in severe SIOD. Development of mild intermittent anemia and thrombocytopenia was consistent with progressive marrow failure, or potentially, suggestive of an unrecognized related autoimmune disorder. Fifty percent of patients exhibit anemia secondary to renal disease and/or autoimmune problems and 40% develop thrombocytopenia.[4] One other reported patient with neutropenia was treated with G-CSF, and, as in our case, neutrophil production increased.[4] Prolonged G-CSF treatment was not predicted to significantly improve our patient's long-term outcome because it would not alleviate T-cell, erythrocyte, or platelet problems.

Multisystem problems in SIOD vary considerably. Morbidity and death are often due to renal failure, immunodeficiency, or cerebral vascular disease. Those severely affected demonstrate in utero growth failure, as did our patient, and often die within the first 3 years of life.[3,4] Currently, no effective treatments for the T-cell deficiency or ischemic cerebral events exist. Kidney transplantation has successfully treated the renal failure. In reports on 11 patients who received kidney transplants, up to 10 years of follow-up data are available for 6 cases. Three patients are still living without disease in the transplanted kidney.[4] They lacked significant immunodeficiency at the time of kidney transplantation. In our patient, severe immunodeficiency (neutropenia and lymphopenia) preceded renal failure, making the risk of complications secondary to kidney transplant–related immunosuppressive therapy extremely high. Given this, management of his marrow failure and immunodeficiency was required before kidney transplantation. BMT was successful in trilineage reconstitution of his marrow, improvement of his overall white blood cell count, and marked reduction of all related systemic complications of bone marrow failure.

His 8-month course of severe GI problems after BMT was related to GI-GVHD, although he had milder GI problems before BMT. A recent SIOD case emphasized significant malabsorption and abdominal pain associated with an autoimmune process.[18] Despite such autoimmune symptoms in SIOD, serology studies have been non-specific, making it difficult to determine whether an underlying autoimmune process was involved in our patient's GI disease. Given his GI symptoms before and after BMT, however, his severe GI symptoms after BMT may have been compounded by his underlying SIOD course. Similarly, it is difficult to define the role of SIOD in his documented hypertensive encephalopathy with demonstration of small vessel ischemia by magnetic resonance imaging after BMT. Whether underlying SIOD-related vascular dis-

ease contributed to development of his ischemic events remains unclear. The literature does not clarify whether cerebral ischemic events reported in SIOD are related to hypertension.[4,6,7] The pathophysiology of these complex multisystem processes merits further consideration in affected individuals to better define and anticipate potential systemic complications associated with SIOD during BMT.

The diagnosis of SIOD with probable autosomal recessive inheritance facilitates recurrence risk counseling for other family members, but no carrier detection or prenatal diagnostic tests exist.[3,4] Although intrauterine growth retardation is noted in the severe form, it is not sensitive or specific enough for establishing a prenatal diagnosis. No medical problems are reported in heterozygous carriers. Our patient's family history is striking for significant nonspecific early-onset cancers, short stature, and autoimmune disorders. Detailed evaluation of obligate carriers in our patient's family and others should help determine whether subtle expression occurs in some heterozygotes.

Highly variable initial symptoms make the diagnosis of SIOD difficult to confirm. The diagnosis is based on a constellation of clinical and laboratory findings (Table). Our patient's unique constellation of early findings and the disease rarity delayed the diagnosis, despite multiple evaluations over 6 years. Fewer than 50 individuals reportedly have SIOD worldwide, which may reflect under-diagnosis because of a lack of knowledge about this condition and the fact that individuals may die before an accurate diagnosis is made. SIOD should be considered in any child with growth failure, skeletal dysplasia, or both associated with marrow hypoplasia, immunodeficiency, and/or progressive proteinuria. Although no single test confirms the diagnosis, skeletal surveys, dysmorphology examinations, serial complete blood counts, immunology evaluations,

Table Clinical findings in our patient compared with other individuals with SIOD

	Boerkoel et al[4]*		Our patient
Feature	r/n	%	
Facial features			
Low nasal bridge	26/32	81	+
Bulbous nasal tip	28/33	85	+
Microdontia	5/13	38	+
Pigmented macules	28/34	82	+
Unusual hair	19/25	76	+
Skeletal features			
Short neck & trunk	30/33	91	+
Lumbar lordosis & protruding abdomen	31/33	94	+
Spondyloepiphyseal dysplasia†	33/33‡	100	+
Ovoid, flat vertebrae	33/34	97	+
Hypoplastic pelvis	26/32	81	+
Abnormal femoral heads	31/33	94	+
Development			
Intellectual delay	6/31	19	–
Motor delay	6/30	20	–
Growth			
Intrauterine growth retardation	26/37	70	+
↓Postnatal growth†	39/39	100	+
Endocrine			
↑Thyroid-stimulating hormone	16/33	48	–
↓Growth hormone	1/19	5	–
Ocular findings			
Corneal opacities	7/26	27	–
Hematology			
Lymphopenia	35/37	95	+
Neutropenia	11/25	44	+
Thrombocytopenia	11/27	41	+
Anemia	18/26	69	+
Immunology			
Recurrent infections	15/31	48	+
Negative skin test results	10/11	91	+
Abnormal immunoglobulin levels	16/24	67	+
Nephrology			
Focal segmental glomerular sclerosis	27/31	87	+
Proteinuria†	39/39	100	+
Nephrotic syndrome	34/36	94	+
Progressive renal failure	30/34	88	+
Congenital structured renal anomaly	1/1‡		+
Hypertension	31/32	97	+
Vascular			
Cerebral ischemia	18/37	49	?
Arteriosclerosis	7/17	41	?
Moyamoya phenomenon	2/11	18	–
Other			
GI disease	1/1‡		+

n, Number of patients in whom the presence or absence of feature was reported; *r;* number of patients who had the reported feature; ↓, decreased; ↑, increased, *GI,* gastrointestinal.
*Modified from Boerkoel et al.[4]
†Major feature of disorder.
‡Not specifically discussed by Boerkoel et al.[4]

bone marrow analyses, and renal studies should lead to the correct diagnosis. Increased awareness of SIOD will assist in making earlier diagnoses, facilitate earlier management, allow better prognostic and anticipatory guidance, and enable appropriate genetic counseling.

Our experience also suggests that BMT along with kidney transplantation may be effective to reduce morbidity related to hematologic, immunologic, and renal problems. Based on findings from our case, BMT does not halt progression of the renal disease and may even accelerate renal problems, given the potential renal toxicities of BMT therapies.[19] Long-term effects of BMT on other systemic aspects of the disease (eg, cerebral ischemia, vascular disease, growth, and autoimmune dysfunction) cannot be determined without longer follow-up and examination in a larger series of similarly treated patients. The continued improvement in our patient at 25 months after BMT and 6 months after kidney transplantation, however, is encouraging and suggests that further exploration of this course of therapy in SIOD is warranted.

We are grateful to our patient and his family for allowing us to share his story and wish to thank the numerous physicians and other health care workers who contributed their expertise to the evaluation and care of this patient. We also thank M. VanOvermeer for her assistance with manuscript preparation.

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